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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07C 401/00, A61K 31/59 — A1

(11) International Publication Number: WO 94/15912

(43) International Publication Date: 21 July 1994 (21.07.94)

(21) International Application Number: PCT/DK94/00011

(22) International Filing Date: 7 January 1994 (07.01.94)

(30) Priority Data:
9300763.1 15 January 1993 (15.01.93) GB

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(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NEW CRYSTALLINE FORM OF A VITAMIN D ANALOGUE

(57) Abstract

The present invention relates to calcipotriol hydrate - a new crystalline form of calcipotriol - with superior technical properties and with superior stability.

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NEW CRYSTALLINE FORM OF A VITAMIN D ANALOGUE

The present invention relates to calcipotriol, hydrate - a new crystalline form of calcipotriol - with superior technical properties e.g. in the manufacture of crystal suspension formulations, and with superior stability properties.

Calcipotriol (INN) (calcipotriene (USAN), (1α,3β,5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochola-5,7,-10(19),22-tetraene-1,3,24-triol) is described in International patent application No. PCT/DK86/00081, filing date 14th July 1986, publication No. WO 87/00834.

Calcipotriol possesses a remarkable profile of biological activity which has proved very useful e.g. in the topical treatment of psoriasis.

Due to the poor stability of calcipotriol in certain solutions it is in some formulations, in particular in creams and gels, preferred to use crystal suspensions.

In order to prepare suitable crystal suspension formulations it is mandatory to be able to control the crystal size, this parameter being important with regard to obtaining a reproducible release of the active compound from the formulation. The crystalline bulk drug is usually subjected to micronization or to a wet milling process in order to reduce the crystal size before the final suspension formulation is prepared.

In the case of calcipotriol a wet ball milling process has been used. However, it has turned out to be technically difficult to perform this process when using the anhydrous crystal form described in WO 87/00834. These crystals are not easily wetted and during the milling process they develop a stable foam which results in difficulties in obtaining a suitable small and uniform particle size.

It has now surprisingly been found that these technical problems can be avoided when a hitherto unknown cry-

stalline form of calcipotriol, i.e. calcipotriol, hydrate, is used instead of the known anhydrous form. The hydrate is technically superior to the anhydrate; it is easily wetted and the wet ball milling process is running smoothly.

This novel product is the monohydrate of calcipotriol which is perfectly crystalline, stable and well suited for its use in modern therapy.

Stability studies have demonstrated that calcipotriol, hydrate is surprisingly stable, and this is illustrated by stability data at 40°C.

The anhydrous form of calcipotriol shows a considerable degree of decomposition at this temperature and more than 30% degradation is seen after 12 months storage.

In contrast the compound of the present invention, calcipotriol hydrate, shows no degradation after 12 months storage at 40°C.

Calcipotriol, monohydrate may be prepared by dissolving crystalline or non-crystalline calcipotriol in an organic solvent, e.g. ethyl acetate or acetone, followed by the addition of water and optionally a non polar solvent, e.g. hexane.

Calcipotriol, monohydrate shall form part of pharmaceutical preparations for topical use, such as creams, ointments, solutions, lotions or gels. The concentration of the active ingredient will generally be between 1 and 100 µg/g.

The formulations will be applied one or more times daily.

The formulations prepared according to the present invention comprise the active compound in association with a pharmaceutically acceptable vehicle and optionally other therapeutic ingredient(s). The vehicle(s) must be "acceptable" in the sense of being compatible with the other ingredients of the preparations and not deleterious to the recipient thereof.

Preparations suitable for topical administration include liquid or semi-liquid preparations such as lini-

ments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments, pastes or gels; or solutions or suspensions.

In addition to the aforementioned ingredients, the preparations of this invention may include one or more additional ingredients such as diluents, buffers, surface active agents, thickeners, lubricants, preservatives, e.g. methyl hydroxybenzoate (including anti-oxidants), emulsifying agents and the like.

The invention will now be further described in the following non-limiting Examples:

Example 1

Calcipotriol (2.5 g) was dissolved in ethyl acetate (80 ml) at 50-80°C and filtered. The solution was saturated with water, and the product precipitated upon voluntary cooling to room temperature. The resulting slurry was cooled to 0-10°C and filtered. The filtered product was dried in vacuo to give calcipotriol, hydrate (2.35 g).

IR spectroscopy KBr technique

Lines characteristic for the hydrate are 1455 (m), 1442 (m), 1330 (w), 1290 (m), 1210 (m), 1085 (m), 907 (m), 895 (m) and 573 (w) cm^{-1}, respectively.

Solid state CPMAS[1] NMR

The following resonances are characteristic for calcipotriol, hydrate: 147.9, 146.5, 134.8, 130.3, 129.0, 126.5, 116.0, 109.4, 75.5, 68.2, 67.2, 56.9, 55.2, 47.8, 47.5, 42.9, 42.0, 41.3, 30.7, 28.9, 25.6, 23.1, 22.6, 19.5, 14.6, 6.2 and 1.9 ppm, respectively.

Differential Scanning Calorimetry (DSC)

On a Perkin Elmer DSC7 instrument using 20°C/min. and approx. 2 mg sample, the hydrate shows loss of water near 117°C and a melting peak near 169.7°C.

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1 Cross Polarization Magic Angle Spinning

Example 2

Calcipotriol (22.7 g) was dissolved in methanol (200-250 ml), filtered and concentrated in vacuo to a residue which was dissolved in ethyl acetate (200-250 ml) at 50-80°C and water (2 ml) was added. The resulting solution was seeded with calcipotriol, hydrate, and the product precipitated upon voluntary cooling to room temperature. Hexane (100 ml) was added from a dropping funnel, the resulting slurry was cooled to 0-10°C and filtered.

The filtered product was washed with a 1:1 mixture of ethyl acetate and hexane (200 ml) and dried in vacuo to give calcipotriol, hydrate (19.7 g), shown to be identical with the product described in Example 1.

Example 3

Calcipotriol (120 mg) was dissolved in acetone (2 ml) and water (1.5-3 ml) was added. The product crystallized spontaneously and the resulting slurry was cooled to 0-10°C and filtered. The filtered product was dried in vacuo to yield calcipotriol, hydrate (100 mg), shown to be identical with the product of Example 1.

Example 4

Cream 50 µg/g

Calcipotriol, hydrate	50 mg
Cetomacrogol 1000	30 g
Cetostearylalcohol	60 g
Chloroallylhexaminium chloride	0.5 g
Propyleneglycol	30 g
Disodiumhydrogenphosphate	2 g
Liquid paraffin	50 g
White soft paraffin	170 g
Purified water	up to 1000 g

Melt cetomacrogol 1000, cetostearylalcohol, liquid paraffin and white soft paraffin at 75°C. Dissolve propylene glycol in water at 75°C and mix the solution with the fatty phase. Homogenize the emulsion and cool to 30°C. Mill calcipotriol, hydrate in part of the aqueous phase to a particle size predominantly below 10 µm and suspend in an aqueous solution of disodiumhydrogenphosphate and chloroallylhexaminiumchloride. Add the suspension to the emulsion and fill the cream in tubes.

Example 5

Gel 50 µg/g

Calcipotriol, hydrate (corresponding to 50 mg anhydrous)		52.2 mg
Carbomer		7 g
Cetomacrogol 1000		1 g
Diazolidinyl urea		2 g
Dichlorobenzyl alcohol		1 g
Disodium edetate		0.5 g
Sodium hydroxide		3.7 g
Propylene glycol		30 g
Purified water	up to	1000 g

Dissolve cetomacrogol, diazolidinyl urea, dichlorobenzyl alcohol, disodium edetate and propylene glycol in water. Add carbomer and homogenize by high speed. Add during agitation sodium hydroxide dissolved in part of the water. Mill the calcipotriol, hydrate in a bottle of water with glass beads until a particle size below 10 µm has been obtained. Add the calcipotriol, hydrate suspension to the gel and mix for 30 minutes. Fill the gel into collapsible tubes.

WHAT WE CLAIM IS:

1. Calcipotriol [2], monohydrate.

2. Pharmaceutical composition containing the compound of claim 1.

3. Pharmaceutical composition according to claim 2 which is a cream.

4. Pharmaceutical composition according to claim 2 which is a gel.

5. Pharmaceutical composition according to any one of claims 2 - 4, with a content of the active component of 1 - 100 μg/g of the composition.

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2 1α,3β,5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1,3,24-triol

INTERNATIONAL SEARCH REPORT

Inter ıal Application No
PCT/DK 94/00011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C401/00 A61K31/59

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,87 00834 (LEO PHARMACEUTICAL PRODUCTS LTD) 12 February 1987 cited in the application see page 12; examples 58,59 see page 40 - page 42; examples 3-7	1-5
A	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS. vol. 171, no. 3 , 28 September 1990 , DULUTH, MINNESOTA US pages 1056 - 1063 M. THAVARAJAH ET AL '1,25(OH)2D3 and Calcipotriol (MC903) Have Similar Effects on The Induction of Osteoclast-Like Cell Formation in Human Bone Marrow Cultures' see the whole document	1-5

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 April 1994	25. 04. 94

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 119, no. 5, 2 August 1993, Columbus, Ohio, US; abstract no. 41719, M. BAGOT ET AL 'Immunosuppressive Effects of 1,25-Dihydroxyvitamin D3 Analog (Calcipotriol) on Epidermal Cells' page 182 ;column 1 ; see abstract & PROC. WORKSHOP VITAM. D (8TH) 1991 pages 518 - 519 ---	1-5
A	CHEMICAL ABSTRACTS, vol. 117, no. 21, 23 November 1992, Columbus, Ohio, US; abstract no. 205159, M. BRAEUTIGAM ET AL 'Effects of Calcipotriol (MC903) and Calcitriol After Topical Application on The Skin of Hairless Rats. Much Lower Effect of Calcipotriol on Systemic Calcium Homeostasis' page 93 ;column 1 ; see abstract & SKIN PHARMACOL. vol. 5, no. 2 , 1992 pages 87 - 92 ---	1-5
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter al Application No
PCT/DK 94/00011

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8700834	12-02-87	AU-B-	603340	15-11-90
		AU-A-	6196186	05-03-87
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